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FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 17:13:14 ON 06 MAR 2000

L1	20861	S MESENCEPHALON
L2	10402	S L1 AND (NEURON OR NEURAL)
L3	61	S L2 AND (IMMORTALIZED OR TRANSFORMED)
L4	24	S L3 AND DOPAMINERGIC
L5	0	S L4 AND GABA
L6	15	DUP REM L4 (9 DUPLICATES REMOVED)
L7	15	SORT L6 PY
L8	89	S L1 AND (IMMORTALIZED OR TRANSFORMED)
L9	1	S L8 AND V-MYC
L10	2	S L1 AND V-MYC
L11	275	S L1 AND ONCOGENE
L12	0	S L11 AND FIBRONECTIN
L13	5	S L11 AND (IMMORTALIZED OR TRANSFORMED)
L14	1	DUP REM L13 (4 DUPLICATES REMOVED)
L15	186	S L2 AND ONCOGENE
L16	12	S L15 AND (PRECURSOR OR PROGENITOR)
L17	7	DUP REM L16 (5 DUPLICATES REMOVED)
L18	7	SORT L17 PY
L19	0	S L15 AND (TRANSFORMED OR IMMORATLIZED)
L20	186	S L15 AND (NEURON OR NEURAL)
L21	5	S L20 AND IMMORTALIZED
L22	1	DUP REM L21 (4 DUPLICATES REMOVED)
L23	59	S L1 AND (IMMORATALIZED OR TRANSFORMED)
L24	32	DUP REM L23 (27 DUPLICATES REMOVED)
L25	32	SORT L24 PY

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L7 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2000 ACS
TI An **immortalized**, type-1 astrocyte of mesencephalic origin source of a **dopaminergic** neurotrophic factor
SO J. Mol. Neurosci. (1999), Volume Date 1998, 11(3), 209-221
CODEN: JMNEES; ISSN: 0895-8696
AU Panchision, David M.; Martin-DeLeon, Patricia A.; Takeshima, Takao; Johnston, Jane M.; Shimoda, Kotaro; Tsoulfas, Pantelis; McKay, Ronald D. G.; Commissiong, John W.
AB Rat embryonic d 14 (E14) mesencephalic cells, 2.5% of which are glioblasts, were incubated in medium contg. 10% of fetal bovine serum for 12 h and subsequently expanded in a serum-free medium using basic fibroblast growth factor (bFGF) as the mitogen. On a single occasion, after more than 15 d in culture, several islets of proliferating, glial-like cells were obsd. in one dish. The cells, when isolated and passaged, proliferated rapidly in either a serum-free or serum-contg. growth medium. Subsequent immunocytochem. anal. showed that they stained pos. for GFAP and vimentin, and neg. for A2B5, O4, GalC, and MAP2. Serum-free conditioned medium (CM) prepd. from these cells caused a fivefold increase in survival and promoted neuritic expansion of E14 mesencephalic **dopaminergic neurons** in culture. These actions are similar to those exerted by CM derived from primary, mesencephalic type-1 astrocytes. The pattern of expression of the region-selective genes; wnt-1, en-1, sis showed that 70% of the cells were heteroploid, and of these, 50% were tetraploid. No apparent decline in proliferative capacity has been obsd. after 25 passages. The properties of this cell line, named ventral mesencephalic cell line one (VMCL1), are consistent with those of an **immortalized**, type-1 astrocyte. The mesencephalic origin of the cell line, and the pattern and potency of the neurotrophic activity exerted by the CM, strongly suggest that the neurotrophic factor(s) identified are novel, and will likely be strong candidates with clin. utility for the treatment of Parkinson's disease.

L7 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2000 ACS
TI Human **mesencephalon** cell lines and methods of use therefor
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
IN Sah, Dinah W.; Raymon, Heather K.
AB Conditionally-immortalized human **mesencephalon** cell lines are provided. Such cell lines, which may be clonal, may be used to generate **neurons**, including **dopaminergic neurons**. The cell lines and/or differentiated cells may be used for the development of therapeutic agents to prevent and treat a variety of neurological diseases such as Parkinson's disease. The cell lines and/or differentiated cells may also be used in assays and for the general study of **mesencephalon** cell development and differentiation.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000009669	A1	20000224	WO 1999-US18403	19990812

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

L7 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2000 ACS
TI Efficacy of grafted **immortalized** dopamine **neurons** in an animal model of Parkinsonism: a review
SO Mol. Genet. Metab. (1998), 65(1), 1-9
CODEN: MGMEFF; ISSN: 1096-7192
AU Prasad, Kedar N.; Clarkson, Edward D.; La Rosa, Francisco G.; Edwards-Prasad, Judith; Freed, Curt R.
AB A review with 66 refs. Dopamine (DA) deficiency is one of the primary lesions in the pathogenesis of Parkinson disease (PD). Because of long-term toxicity of L-DOPA therapy, the grafting of fetal mesencephalic tissue contg. dopamine **neurons** or homogeneous populations of DA **neurons** into striatum appears to be rational. Fetal tissue transplants have many problems which include legal (in some countries), ethical, paucity of tissue availability, heterogenicity of cell populations, and the presence of antigen-presenting cells that are responsible for rejection of allogeneic grafts. To resolve the above problems, the authors have established **immortalized** DA **neurons** from fetal rat **mesencephalon** by inserting the large T-antigen (LTa) gene of the SV40 virus into the cells. A clone of DA **neurons** (1RB3AN27) was isolated, characterized, and tested in 6-hydroxydopamine (6-OHDA)-lesioned rats (a model of PD). These cells divided with a doubling time of about 26 h, expressed the LTa gene, and contained the tyrosine hydroxylase and dopamine transporter proteins and their resp. mRNAs, which became elevated upon differentiation. These cells were nontumorigenic and nonimmunogenic and improved the symptoms of neurol. deficits (methamphetamine-induced rotation) in 6-OHDA-lesioned rats. The differentiated DA **neurons** were more effective than undifferentiated ones. These studies suggest that **immortalized** DA **neurons** generated in vitro by LTa gene insertion may be used in transplant therapy without fear of tumor formation or rejection. (c) 1998 Academic Press.

I.7 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS

TI Large T-antigen **immortalized** embryonic rat **mesencephalon** survives transplantation, does not form tumors, and produces behavioral improvement in a rat model of Parkinson's disease.

SO Journal of Investigative Medicine, (1997) Vol. 45, No. 1, pp. 109A.
Meeting Info.: Meeting of the American Federation for Medical Research, Western Regional Carmel, California, USA February 5-8, 1997
ISSN: 1081-5589.

AU Weiland, D. A. (1); Clarkson, E. D. (1); Kaddis, F. G. (1); La Rosa, F. G.; Edwards-Prasad, J.; Freed, C. R. (1); Prasad, K. N.

ANSWER 4 OF 15 MEDLINE

TI Evidence for a novel neurotrophic factor for **dopaminergic** **neurons** secreted from mesencephalic glial cell lines.

SO JOURNAL OF NEUROSCIENCE RESEARCH, (1996 Mar 1) 43 (5) 576-86.
Journal code: KAC. ISSN: 0360-4012.

AU Engele J; Rieck H; Choi-Lundberg D; Bohn M C

AB Our previous studies have shown that primary mesencephalic glia secrete factors that promote **dopaminergic** cell survival and differentiation in vitro. To obtain enough starting material to identify the neurotrophic activity, embryonic day (E)14.5 rat mesencephalic glia were stimulated with acidic fibroblast growth factor to increase number of cells. These cells were replated in the absence of **neurons** and **immortalized** by transfection with the SV 40 large T-antigen. Clonal cell lines were established and characterized for immunoreactivity (IR) to various glial and non-glial markers. Media conditioned by these cell lines were tested for survival-promoting effects on **dopaminergic** **neurons** in serum-free cultures of the dissociated E14.5 rat **mesencephalon**. All cell lines expressed IR for the astrocytic marker, GFAP, the oligodendroglial marker, CNP, and for A2B5, a marker for O-2A progenitor cells, but were negative for the neuronal marker, microtubule associated protein-2, and the fibroblast marker, fibronectin. Moreover, treatment of serum-free cultures of the dissociated E14.5 **mesencephalon** with glial cell line-CM conditioned medium (CM) delayed **dopaminergic** cell death in a dose-dependent manner, resulting in a maximal twofold to sixfold increase in the number of surviving tyrosine hydroxylase-IR **neurons** at various days in vitro. This increase in **dopaminergic** cell survival was not mimicked by GDNF, BDNF or NT-3 within the initial 3 days of cultivation. Moreover, initial biochemical characterization demonstrated that the neurotrophic activity is restricted to the high MW fraction of >50 kD of glial cell line-CM. Since the apparent MW of this factor exceeds the size of most known growth factors, it may represent a novel **dopaminergic** neurotrophic factor.

L10 ANSWER 1 OF 2 MEDLINE
TI Cloned microglial cells but not macrophages synthesize beta-endorphin in response to CRH activation.
SO GLIA, (1993 Dec) 9 (4) 305-10.
Journal code: GLI. ISSN: 0894-1491.
AU Sacerdote P; Denis-Donini S; Paglia P; Granucci F; Panerai A E; Ricciardi-Castagnoli P
AB The properties of microglial cell clones, obtained from embryonic mouse brain primary cultures immortalized with recombinant retroviruses, have been investigated and compared with the properties of macrophage clones similarly obtained. Macrophage clones differed from microglial clones in some functions but shared most of the immunological properties. Interestingly, microglial cells were able to produce beta-endorphin, and this production was regulated differently in microglial cell clones when compared with macrophages clones. Although lipopolysaccharide (LPS) treatment induces an increase in beta-endorphin concentration in both cell types, only microglial clones and primary microglial cell cultures respond to the neuroendocrine stimulus corticotropin releasing hormone (CRH). In addition, in these cells, beta-endorphin release is regulated by a classical neurotransmitter, such as noradrenaline, adding some evidence of communication between neurons and microglial cells.

L10 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2000 BIOSIS
TI Pattern of gene induction by dopamine agonists in rat midbrain cultures studied by microarray analysis.
SO Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 331. Meeting Info.: 29th Annual Meeting of the Society for Neuroscience, Part 1 Miami Beach, Florida, USA October 23-28, 1999 The Society for Neuroscience . ISSN: 0190-5295.
AU Soussis, I. A. (1); Mytilineou, C. (1); Olanow, C. W. (1); Sealfon, S. C. (1)

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L13	5	S L11 AND (IMMORTALIZED OR TRANSFORMED)
L14	1	DUP REM L13 (4 DUPLICATES REMOVED)

L22 ANSWER 1 OF 1 MEDLINE DUPLICATE 1

TI Methamphetamine induces apoptosis in **immortalized neural** cells: protection by the proto-**oncogene**, bcl-2.

SO SYNAPSE, (1997 Feb) 25 (2) 176-84.
Journal code: VFL. ISSN: 0887-4476.

AU Cadet J L; Ordonez S V; Ordonez J V

AB Methamphetamine (METH) is an amphetamine analog that produces degeneration of the dopaminergic system in mammals. The neurotoxic effects of the drug are thought to be mediated by oxygen-based free radicals. In the present report, we have used **immortalized neural** cells obtained from rat **mesencephalon** in order to further assess the role of oxidative stress in METH-induced neurotoxicity. We thus tested if the anti-death proto-**oncogene**, bcl-2 could protect against METH-induced cytotoxicity. METH caused dose-dependent loss of cellular viability in control cells while bcl-2-expressing cells were protected against these deleterious effects. Using flow cytometry, immunofluorescent staining, and DNA electrophoresis, we also show that METH exposure can cause DNA strand breaks, chromatin condensation, nuclear fragmentation, and DNA laddering. All these changes were prevented by bcl-2 expression. These observations provide further support for the involvement of oxidative stress in the toxic effects of amphetamine analogs. They also document that METH-induced cytotoxicity is secondary to apoptosis. These findings may be of relevance to the cause(s) of Parkinson's disease which involves degeneration of the nigrostriatal dopaminergic pathway.

ANSWER 28 OF 32 MEDLINE

TI A truncated SV40 large T antigen lacking the p53 binding domain overcomes p53-induced growth arrest and immortalizes primary mesencephalic cells.

SO CELL AND TISSUE RESEARCH, (1998 Feb) 291 (2) 175-89.
Journal code: CQD. ISSN: 0302-766X.

AU Truckenmiller M E; Tornatore C; Wright R D; Dillon-Carter O; Meiners S; Geller H M; Freed W J

AB As an alternative to primary fetal tissue, immortalized central nervous system (CNS)-derived cell lines are useful for in vitro CNS model systems and for gene manipulation with potential clinical use in neural transplantation. However, obtaining immortalized cells with a desired phenotype is unpredictable, because the molecular mechanisms of growth and differentiation of CNS cells are poorly understood. The SV40 large T antigen is commonly used to immortalize mammalian cells, but it interferes with multiple cell-cycle components, including p53, p300, and retinoblastoma protein, and usually produces cells with undifferentiated phenotypes. In order to increase the phenotypic repertoire of immortalized CNS cells and to address the molecular mechanisms underlying immortalization and differentiation, we constructed an expression vector containing a truncated SV40 large T gene that encodes only the amino-terminal 155 amino acids (T155), which lacks the p53-binding domain. Constructs were first transfected into a p53-temperature-sensitive cell line, T64-7B. Colonies expressing T155 proliferated at the growth-restrictive temperature. T155 was then transfected into primary cultures from embryonic day-14 rat **mesencephalon**. Two clonal cell lines were derived, AF-5 and AC-10, which co-expressed T155 and mature neuronal and astrocytic markers. Thus, the amino-terminal portion of SV40 large T is sufficient to: (1) overcome p53-mediated growth arrest despite the absence of a p53-binding region, and (2) immortalize primary CNS cells expressing mature markers while actively dividing. T155 and T155-transfectants may be useful for further studies of cell-cycle mechanisms and phenotyic expression in CNS cells or for further gene manipulation to produce cells with specific properties.

L25 ANSWER 26 OF 32 MEDLINE

TI Efficacy of grafted immortalized dopamine neurons in an animal model of parkinsonism: a review.

SO MOLECULAR GENETICS AND METABOLISM, (1998 Sep) 65 (1) 1-9. Ref: 66
Journal code: CXY. ISSN: 1096-7192.

AU Prasad K N; Clarkson E D; La Rosa F G; Edwards-Prasad J; Freed C R

AB Dopamine (DA) deficiency is one of the primary lesions in the pathogenesis of Parkinson disease (PD). Because of long-term toxicity of L-DOPA therapy, the grafting of fetal mesencephalic tissue containing dopamine neurons or homogeneous populations of DA neurons into striatum appears to be rational. Fetal tissue transplants have many problems which include legal (in some countries), ethical, paucity of tissue availability, heterogenicity of cell populations, and the presence of antigen-presenting cells that are responsible for rejection of allogeneic grafts. In order to resolve the above problems, we have established immortalized DA neurons from fetal rat **mesencephalon** by inserting the large T-antigen (LTa) gene of the SV40 virus into the cells. A clone of DA neurons (1RB3AN27) was isolated, characterized, and tested in 6-hydroxydopamine (6-OHDA)-lesioned rats (a model of PD). These cells divided with a doubling time of about 26 h, expressed the LTa gene, and contained the tyrosine hydroxylase and dopamine transporter proteins and their respective mRNAs, which became elevated upon differentiation. These cells were nontumorigenic and nonimmunogenic and improved the symptoms of neurological deficits (methamphetamine-induced rotation) in 6-OHDA-lesioned rats. The differentiated DA neurons were more effective than undifferentiated ones. These studies suggest that immortalized DA neurons generated in vitro by LTa gene insertion may be used in transplant therapy without fear of tumor formation or rejection. Copyright 1998 Academic Press.

L25 ANSWER 20 OF 32 MEDLINE
TI Characterization and transplantation of two neuronal cell lines with dopaminergic properties.
SO NEUROCHEMICAL RESEARCH, (1996 May) 21 (5) 619-27.
Journal code: NX9. ISSN: 0364-3190.
AU Adams F S; La Rosa F G; Kumar S; Edwards-Prasad J; Kentroti S; Vernadakis A; Freed C R; Prasad K N
AB Immortalized rat mesencephalic cells (1RB3AN27) produced dopamine (DA) at a level that was higher than produced by undifferentiated or differentiated murine neuroblastoma cells (NBP2) in culture. Treatment of 1RB3AN27 and NBP2 cells with a cAMP stimulating agent increased tyrosine hydroxylase (TH) activity and the intensity of immunostaining for the DA transporter protein (DAT). 1RB3AN27 cells were labelled with primary antibodies to neuron specific enolase (NSE) and nestin and exhibited very little or no labeling with anti-glial fibrillary acidic protein (GFAP). 1RB3AN27 cells exhibited beta- and alpha-adrenoreceptors, and prostaglandin E1 receptors, all of which were linked to adenylate cyclase (AC). Dopamine receptor (D1) and cholinergic muscarinic receptors linked to AC were not detectable. The levels of PKC alpha and PKC beta isoforms were higher than those of PKC gamma and PKC delta in 1RB3AN27 cells. The 1RB3AN27 cells were more effective in reducing the rate of methamphetamine-induced turning in rats with unilateral 6-OHDA lesion of the nigrostriatal system than differentiated NBP2 cells. The grafted 1RB3AN27 were viable as determined by DiI labelling, but they did not divide and did not produce T-antigen protein; however, when these grafted cells were cultured in vitro, they resumed production of T-antigen and proliferated after the primary glia cells and neurons of host brain died due to maturation and subsequent degeneration. Examination of H&E stained sections of the grafted sites revealed no evidence of infiltration of inflammatory cells in the grafted area suggesting that these cells were not immunogenic. They also did not form tumors.

L25 ANSWER 15 OF 32 MEDLINE

TI Establishment and characterization of immortalized clonal cell lines from fetal rat mesencephalic tissue.

SO IN VITRO CELLULAR AND DEVELOPMENTAL BIOLOGY. ANIMAL, (1994 Sep) 30A (9) 596-603.
Journal code: BZE. ISSN: 1071-2690.

AU Prasad K N; Carvalho E; Kentroti S; Edwards-Prasad J; Freed C; Vernadakis A

AB This investigation reports for the first time the establishment of immortalized clones of dopamine-producing nerve cells in culture. Freshly prepared single-cell suspensions from fetal (12-day-old) rat mesencephalic tissue were transfected with plasmid vectors, pSV3neo and pSV5neo, using an electroporation technique. Cells were plated in tissue culture dishes which were precoated with a special substrate and contained modified MCDB-153 growth medium with 10% heat inactivated fetal bovine serum. The immortalized cells were selected by placing the transfected cells in a selection medium (modified MCDB-153 containing 400 micrograms/ml geneticin). The survivors showed the presence of T-antigens and were non-tumorigenic. Two cell lines, 1RB3 derived from cells transfected with pSV3neo, and 2RB5 derived from cells transfected with pSV5neo revealed only 1 to 2% tyrosine hydroxylase (TH)-positive cells. Repeated single-cell cloning of these cell lines by a standard technique failed to increase the number of TH-positive cells in any clones. Using three cycles of growth, alternating between hormone-supplemented, serum-free medium and serum-containing medium produced a cell line (1RB3A) that was very rich in TH-positive cells. The recloning of 1RB3A yielded clones some of which contained over 95% TH-positive cells. These cells produced homovanillic acid, a metabolite of dopamine, and may be useful not only for neural transplant but also for basic neurobiological studies.

L25 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2000 ACS

TI Two simian virus 40 (SV40)-**transformed** cell lines from the mouse striatum and **mesencephalon** presenting astrocytic characters. I. Immunological and pharmacological properties

SO Dev. Brain Res. (1986), 26(1), 11-22
CODEN: DBRRDB; ISSN: 0165-3806

AU Moura Neto, V.; Mallat, M.; Chneiweiss, H.; Premont, J.; Gros, F.; Prochiantz, A.

AB Dissoc. cultures were initiated from embryonic rostral mesencephalic and striatal tissues dissected from the mouse brain and previously incubated with a simian virus 40 (SV40) suspension. After several weeks in culture, foci of rapidly dividing cells were resuspended and cloned by successive dilns. Several clones expressing the SV40 nuclear T antigen were obtained by these procedures and 2 of them, 1 mesencephalic (F7-Mes) and 1 striatal (F12-Str), were screened for the expression of glial or neuronal characters. Both clones possess adenylate cyclase-linked .beta.2-adrenergic receptors. They also take up and synthesize GABA in amts. compatible with a glial origin. As is the case for astrocytes, the uptake of GABA is inhibited by .beta.-alanine and rather insensitive to the presence of diaminobutyric acid, a specific inhibitor of the neuronal GABA carrier. The most convincing evidence that F7-Mes and F12-Str belong to the astrocytic lineage comes from the fact that the 2 cell lines synthesize glial fibrillary acidic protein as demonstrated by immunofluorescence and immunoblotting.

L25 ANSWER 5 OF 32 SCISEARCH COPYRIGHT 2000 ISI (R)
TI 2 SIMIAN-VIRUS 40 (SV40)-**TRANSFORMED** CELL-LINES FROM THE MOUSE STRIATUM AND **MESENCEPHALON** PRESENTING ASTROCYTIC CHARACTERS .3. A LIGHT AND ELECTRON-MICROSCOPIC STUDY
SO DEVELOPMENTAL BRAIN RESEARCH, (1986) Vol. 26, No. 1, pp. 33-47.
AU AUTILLOTOUATI A (Reprint); MALLAT M; ARAUD D; NETO V M; VUILLET J; GLOWINSKI J; SEITE R; PROCHIANTZ A

L25 ANSWER 6 OF 32 SCISEARCH COPYRIGHT 2000 ISI (R)
TI 2 SIMIAN-VIRUS 40 (SV40)-**TRANSFORMED** CELL-LINES FROM THE MOUSE STRIATUM AND **MESENCEPHALON** PRESENTING ASTROCYTIC CHARACTERS .2. INTERACTIONS WITH MESENCEPHALIC NEURONS
SO DEVELOPMENTAL BRAIN RESEARCH, (1986) Vol. 26, No. 1, pp. 23-31.
AU MALLAT M (Reprint); NETO V M; GROS F; GLOWINSKI J; PROCHIANTZ A

L25 ANSWER 7 OF 32 SCISEARCH COPYRIGHT 2000 ISI (R)
TI 2 SIMIAN-VIRUS 40 (SV40)-**TRANSFORMED** CELL-LINES FROM THE MOUSE STRIATUM AND **MESENCEPHALON** PRESENTING ASTROCYTIC CHARACTERS .1. IMMUNOLOGICAL AND PHARMACOLOGICAL PROPERTIES
SO DEVELOPMENTAL BRAIN RESEARCH, (1986) Vol. 26, No. 1, pp. 11-22.
AU NETO V M; MALLAT M (Reprint); CHNEIWEISS H; PREMONT J; GROS F; PROCHIANTZ A

L25 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2000 ACS
TI Two simian virus 40 (SV40)-**transformed** cell lines from the mouse striatum and **mesencephalon** presenting astrocytic characters. I. Immunological and pharmacological properties
SO Dev. Brain Res. (1986), 26(1), 11-22
CODEN: DBRRDB; ISSN: 0165-3806
AU Moura Neto, V.; Mallat, M.; Chneiweiss, H.; Premont, J.; Gros, F.; Prochiantz, A.
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L25 ANSWER 4 OF 32 MEDLINE

TI Two simian virus 40 (SV40)-**transformed** cell lines from the mouse striatum and **mesencephalon** presenting astrocytic characters. I. Immunological and pharmacological properties.

SO BRAIN RESEARCH, (1986 Apr) 391 (1) 11-22.
Journal code: B5L. ISSN: 0006-8993.

AU Moura Neto V; Mallat M; Chneiweiss H; Premont J; Gros F; Prochiantz A

AB Dissociate cultures were initiated from embryonic rostral mesencephalic and striatal tissues dissected from the mouse brain and previously incubated with a simian virus 40 (SV40) suspension. After several weeks in culture foci of fastly dividing cells were resuspended and cloned by successive dilutions. Several clones expressing the SV40 nuclear T antigen were obtained by these procedures and two of them, one mesencephalic (F7-Mes) and one striatal (F12-Str) were screened for the expression of glial or neuronal characters. Both clones possess adenylate cyclase-linked beta 2-adrenergic receptors. They also take up and synthesize gamma-aminobutyric acid (GABA) in amounts compatible with a glial origin. As is the case for astrocytes, the uptake of GABA is inhibited by beta-alanine and rather insensitive to the presence of diaminobutyric acid (DABA), a specific inhibitor of the neuronal GABA carrier. The most convincing evidence that F7-Mes and F12-Str belong to the astrocytic lineage comes from the fact that the two cell lines synthesize glial fibrillary acidic protein (GFAP) as demonstrated by immunofluorescence and immunoblotting. In an accompanying paper we also show that these lines behave like astrocytes when considered from the point of view of neuroglial interactions.

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J Neurosci Res 1996 Mar 1;43(5):576-86

Evidence for a novel neurotrophic factor for dopaminergic neurons secreted from mesencephalic glial cell lines.

Engele J, Rieck H, Choi-Lundberg D, Bohn MC

Anatomie und Zellbiologie, Universitat Ulm, Germany.

Our previous studies have shown that primary mesencephalic glia secrete factors that promote dopaminergic cell survival and differentiation in vitro. To obtain enough starting material to identify the neurotrophic activity, embryonic day (E)14.5 rat mesencephalic glia were stimulated with acidic fibroblast growth factor to increase number of cells. These cells were replated in the absence of neurons and immortalized by transfection with the SV 40 large T-antigen. Clonal cell lines were established and characterized for immunoreactivity (IR) to various glial and non-glial markers. Media conditioned by these cell lines were tested for survival-promoting effects on dopaminergic neurons in serum-free cultures of the dissociated E14.5 rat mesencephalon. All cell lines expressed IR for the astrocytic marker, GFAP, the oligodendroglial marker, CNP, and for A2B5, a marker for O-2A progenitor cells, but were negative for the neuronal marker, microtubule associated protein-2, and the fibroblast marker, fibronectin. Moreover, treatment of serum-free cultures of the dissociated E14.5 mesencephalon with glial cell line-CM conditioned medium (CM) delayed dopaminergic cell death in a dose-dependent manner, resulting in a maximal twofold to sixfold increase in the number of surviving tyrosine hydroxylase-IR neurons at various days in vitro. This increase in dopaminergic cell survival was not mimicked by GDNF, BDNF or NT-3 within the initial 3 days of cultivation. Moreover, initial biochemical characterization demonstrated that the neurotrophic activity is restricted to the high MW fraction of >50 kD of glial cell line-CM. Since the apparent MW of this factor exceeds the size of most known growth factors, it may represent a novel dopaminergic neurotrophic factor.

PMID: 8833092, UI: 96429942

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In Vitro Cell Dev Biol Anim 1994 Sep;30A(9):596-603

Establishment and characterization of immortalized clonal cell lines from fetal rat mesencephalic tissue.

Prasad KN, Carvalho E, Kentroti S, Edwards-Prasad J, Freed C, Vernadakis A

Center for Vitamins and Cancer Research, School of Medicine, University of Colorado Health Sciences Center, Denver 80262.

This investigation reports for the first time the establishment of immortalized clones of dopamine-producing nerve cells in culture. Freshly prepared single-cell suspensions from fetal (12-day-old) rat mesencephalic tissue were transfected with plasmid vectors, pSV3neo and pSV5neo, using an electroporation technique. Cells were plated in tissue culture dishes which were precoated with a special substrate and contained modified MCDB-153 growth medium with 10% heat inactivated fetal bovine serum. The immortalized cells were selected by placing the transfected cells in a selection medium (modified MCDB-153 containing 400 micrograms/ml geneticin). The survivors showed the presence of T-antigens and were non-tumorigenic. Two cell lines, 1RB3 derived from cells transfected with pSV3neo, and 2RB5 derived from cells transfected with pSV5neo revealed only 1 to 2% tyrosine hydroxylase (TH)-positive cells. Repeated single-cell cloning of these cell lines by a standard technique failed to increase the number of TH-positive cells in any clones. Using three cycles of growth, alternating between hormone-supplemented, serum-free medium and serum-containing medium produced a cell line (1RB3A) that was very rich in TH-positive cells. The recloning of 1RB3A yielded clones some of which contained over 95% TH-positive cells. These cells produced homovanillic acid, a metabolite of dopamine, and may be useful not only for neural transplant but also for basic neurobiological studies.

PMID: 7820310, UI: 95120206

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J Neurosci 1995 Oct;15(10):6666-78

The adult CNS retains the potential to direct region-specific differentiation of a transplanted neuronal precursor cell line.

Shihabuddin LS, Hertz JA, Holets VR, Whittemore SR

Neuroscience Program, University of Miami School of Medicine, Florida 33136, USA.

The chronic survival and differentiation of the conditionally immortalized neuronal cell line, RN33B, was examined following transplantation into the adult and neonatal rat hippocampus and cerebral cortex. In clonal culture, differentiated RN33B cells express p75NTR and trkB mRNA and protein, and respond to brain-derived neurotrophic factor treatment by inducing c-fos mRNA. Transplanted cells, identified using immunohistochemistry to detect beta-galactosidase expression, were seen in most animals up to 24 weeks posttransplantation (the latest time point examined). Stably integrated cells with various morphologies consistent with their transplantation site were observed. In the cerebral cortex, many RN33B cells differentiated with morphologies similar to pyramidal neurons and stellate cells. In the hippocampal formation, many RN33B cells assumed morphologies similar to pyramidal neurons characteristic of CA1 and CA3 regions, granular cell layer neurons of the dentate gyrus, and polymorphic neurons of the hilar region. Identical morphologies were observed in both adult and neonatal hosts, although a greater percentage of beta-galactosidase immunoreactive cells had differentiated in the neonatal brains. These results suggest that RN33B cells have the developmental plasticity to respond to local microenvironmental signals and that the adult brain retains the capacity to direct the differentiation of neuronal precursor cells in a direction that is consistent with that of endogenous neurons.

PMID: 7472427, UI: 96033758

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Proc Natl Acad Sci U S A 1996 Feb 20;93(4):1518-23

Differentiation of the immortalized adult neuronal progenitor cell line HC2S2 into neurons by regulatable suppression of the v-myc oncogene.

Hoshimaru M, Ray J, Sah DW, Gage FH

Laboratory of Genetics, The Salk Institute for Biological Studies, San Diego, CA 92186-5800, USA.

A regulatable retroviral vector in which the v-myc oncogene is driven by a tetracycline-controlled transactivator and a human cytomegalovirus minimal promoter fused to a tet operator sequence was used for conditional immortalization of adult rat neuronal progenitor cells. A single clone, HC2S2, was isolated and characterized. Two days after the addition of tetracycline, the HC2S2 cells stopped proliferating, began to extend neurites, and expressed the neuronal markers tau, NeuN, neurofilament 200 kDa, and glutamic acid decarboxylase in accordance with the reduced production of the v-myc oncoprotein. Differentiated HC2S2 cells expressed large sodium and calcium currents and could fire regenerative action potentials. These results suggest that the suppression of the v-myc oncogene may be sufficient to make proliferating cells exit from cell cycles and induce terminal differentiation. The HC2S2 cells will be valuable for studying the differentiation process of neurons.

PMID: 8643664, UI: 96202311

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C12N 5/00 — A1

(11) International Publication Number: WO 91/09936

(43) International Publication Date: 11 July 1991 (11.07.91)

(21) International Application Number: PCT/US90/07630

(22) International Filing Date: 21 December 1990 (21.12.90)

(30) Priority data:
456,757 26 December 1989 (26.12.89) US

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(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: PROLIFERATED NEURON PROGENITOR CELL PRODUCT AND PROCESS

(57) Abstract

This invention is based on the development of procedures for isolation and proliferation of neuron progenitor cells and is directed to growth, storage, production and implantation of proliferated neuron progenitor cells. The isolation and culture methods are designed to proliferate mammalian ventral mesencephalon neuron progenitor cells *in vitro* to produce a culture which differentiates to produce dopamine-producing cells. The products of this invention include a culture containing neuron progenitor cells, preferably, grown as aggregates in suspension cultures. The process of this invention for preparing neuron progenitor cells comprises obtaining ventral mesencephalon tissue from a donor at the appropriate stage of embryonic development; dissociation of the tissue to obtain single cells and small cell clusters for culture; culturing the neuron progenitor cells in an initial culture medium which selects for a novel cell culture containing neuron progenitor cells and growing the cells for a period of time in a second medium, during which the neuron progenitor cells proliferate.